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Frightening symptom hemoptysis: analysis of etiology, mortality, and treatment outcomes in a large cohort from the chest disease center in Turkiye

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ABSTRACT

Aims: Hemoptysis can indicate serious, potentially life-threatening conditions. The etiology varies by region and can include tuberculosis (TB) in developing countries and malignancies in developed regions.

Methods: This retrospective cohort study reviewed medical records of 400 hospitalized hemoptysis patients between June 2012 and March 2016. Data collected included patient demographics, comorbidities, hemoptysis volume, diagnostic tests, treatments, and outcomes. Survival rates and readmissions were tracked for 2-6 years post-discharge.

Results: Of the 400 patients, 88 (22%) were female and 312 (78%) were male. The leading causes of hemoptysis were bronchiectasis (14%), sequela of tuberculosis (TB sequelae; 19%), and malignancy (22.8%). The most common causes in male patients were lung cancer (27.2%) and TB sequelae (21.8%). Bronchiectasis accounted for 28.4% of cases in female patients, followed by drug-induced hemoptysis at 14.8%. The in-hospital mortality rate was 1% (n=4), with severe hemoptysis present in all four patients who died during admission for hemoptysis. The 2–6-year survival rate was 70.8% for women and 56.1% for men (p=0.005). The factors found to significantly worsen mortality risk were lung malignancy, age >65, diabetes, and chronic obstructive pulmonary disease (COPD).

Conclusion: Overall, lung cancer was found to be the leading cause of hemoptysis, with bronchiectasis being the leading cause in female patients and malignancy in male patients. Close monitoring of male patients is crucial due to higher mortality risk. Careful assessment of patients with hemoptysis having comorbidities such as diabetes and COPD is required due to the reduced survival rates associated with these conditions. Early detection and intervention for lung cancer are essential to optimize the prognosis of affected individuals.

Keywords: Hemoptysis, malignancy, survival rate

INTRODUCTION

Any instance of hemoptysis should be considered serious with prompt evaluation and treatment as it might indicate a life-threatening condition.[1] The etiology of hemoptysis and the percentage of cases attributable to each cause varies. Factors associated with these differences include the geographical region, the quantity of bleeding, and diagnostic techniques used.[2] Previous research has shown that hemoptysis is predominantly caused by tuberculosis (TB) and its effects in developing countries such as India.[3] However, in developed countries, hemoptysis is mostly caused by cancer. This may be due to the general increase in the prevalence of cancer, modern industrial lifestyle, higher use of tobacco products, and greater exposure to environmental toxins in these countries.[2,4]

The diagnosis of hemoptysis requires a comprehensive approach and includes recording the medical history, physical examination, laboratory tests, and the use of imaging modalities such as chest X-ray, computed tomography (CT), and bronchoscopy.[1] Use of some of these methods is contingent upon the resources of each health center, the proficiency of the treating clinician, and the stability of the patient's condition. Bronchoscopic procedures are crucial for patients who require airway control. Utilizing CT and bronchoscopy increases the likelihood of identifying the underlying cause of a patient's hemoptysis.[1,5] Hemoptysis management is determined by the severity of the bleeding and root cause.[6] It is crucial to prioritize the protection of the airway in patients

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experiencing hemoptysis. Therefore, an interdisciplinary treatment approach is required. Antifibrinolytic medications are recommended for mild bleeding, while more severe cases may require therapies such as fiberoptic bronchoscopy (FOB) and local topical vasoconstrictive agents such as epinephrine or balloon blockers.[1,7] Moreover, bleeding can be mitigated by utilizing interventional techniques such as bronchial artery embolization (BAE), therapeutic bronchoscopic procedures, surgery, or a combination of these approaches.[6,7] Several studies have demonstrated that endobronchial treatment and BAE have a positive impact on patient survival.[8,9]

This study aimed to investigate various hemoptysis etiologies, evaluate the efficacy of current diagnostic testing methods, explore treatment options, and identify the factors that affect mortality risk. Our broader objective was to contribute to and enhance our current comprehension of the diverse hemoptysis etiologies and the therapeutic approaches to treatment. Our secondary objective was to identify differences between the sexes that might potentially contribute to the development of more personalized treatment plans. Timely identification and management of hemoptysis can substantially impact patient prognosis and life-threatening ramifications.

METHODS

The study was carried out with the permission of the İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (Date: 21.06.2016 Decision No: 2016/26). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In this. In this single-center retrospective cohort study, the medical records of 7.076 patients presenting to the emergency department with hemoptysis were comprehensively evaluated. From this group, a cohort of 452 patients hospitalized for hemoptysis between June 2012 and March 2016 was identified. Fifty-two patients were excluded from the study due to the absence of a postero-anterior chest X-ray or because they were under 18 or over 90 years old. As a result, the final sample consisted of 400 patients who were hospitalized with primary complaints of hemoptysis over a 4-year period. The study design is summarized in the flowchart shown in Figure 1.

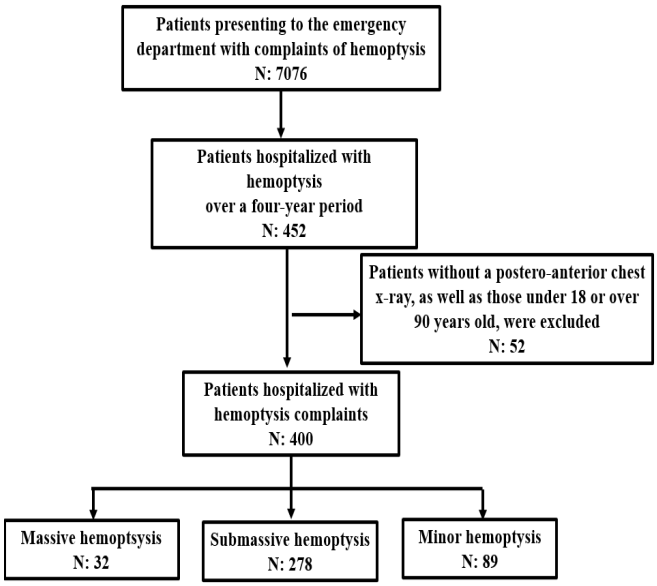
Patients presenting to the emergency department with complaints of hemoptysis
N: 7076
Patients hospitalized with hemoptysis over a four-year period
N: 452
Patients without a postero-anterior chest x-ray, as well as those under 18 or over 90 years old, were excluded
N: 52
Patients hospitalized with hemoptysis complaints
N: 400
Massive hemoptsysis
N: 32
Submassive hemoptysis
N: 278
Minor hemoptysis
N: 89

Figure 1. A flowchart presenting an overview of the study design is provided.

Participants' gender, age, medical histories, prescriptions, drug use (including anticoagulants, vitamin K antagonists, and platelet antiaggregant), test findings, history of hemoptysis, and treatment were all examined. Chest X-rays and, if available, chest CT scan results were documented. Hemoptysis was classified into three categories based on blood expectoration: minor (<50 ml/day), submissive (50–200 ml/day), and massive (>200 ml/day). For hemoptysis, patients received conservative treatment with antitussives, antibiotics, and tranexamic acid (TXA). In addition, the fundamental cause such as, tuberculosis was treated in accordance with the disease's care regimen. In other situations, supportive treatments such as airway protection, the placement of an endotracheal tube, and the administration of blood products were employed alongside invasive procedures such as endobronchial therapy with FOB or rigid bronchoscopy (RB), BAE, and surgery.

Patients diagnosed based on the findings of investigations and disease histories were documented. If a diagnosis could not be established by CT or diagnostic testing and the patient was taking anticoagulants or antiplatelets, the cause of hemoptysis was assumed to be drug-induced. All patients with unexplained hemoptysis and normal radiologic imaging were classified as having "cryptogenic hemoptysis." All in-hospital deaths from hemoptysis were recorded. The survival rates and frequency of hospital readmission for post discharge hemoptysis were tracked.

The patients were followed up for 2–6 years after they were discharged by analysis of their hospital registry records. The hospital's death notification system records for 2018 was used to determine the survival rates among our cohort. The endpoint for overall survival was death from all causes. During the follow-up period, any hospital readmissions due to post discharge hemoptysis we also documented. This data gathered shed light on the long-term prognoses of patients with hemoptysis.

Statistical Analysis

Was carried out using IBM SPSS Statistics for Windows version 23 (IBM Corp., Armonk, NY, USA). Categorical variables were examined using frequency distributions, while numerical variables were studied using descriptive statistics (mean, standard deviation, and median IQR). Categorical variables were compared using the chi-square and Fisher's exact tests. The Kaplan–Meier approach was used to determine survival rates. The log-rank test was used to identify the independent effects on overall survival. Cox regression was used to determine the effect of all covariates on overall survival. A p-value <0.05 was considered statistically significant.

RESULTS

Overall, 400 patients aged 18-90 years who were hospitalized for hemoptysis between June 2012 and March 2016 were included in this study. Of these patients, 312 (78%) were male and the mean age was 55.34±16.09 years (range 18-89). The most common comorbidities were hypertension (n=85, 21.3%) and chronic obstructive pulmonary disease (COPD) (n=65, 16.3%). Tuberculosis and malignancy were more prevalent in the male group (p <0.001, p=0.015), whereas asthma and bronchiectasis were more common in the female group (p=0.008, p=0.003) as etiologies of hemoptysis. A smoking

history was reported in 295 of the 400 (73.7%) patients, with a statistically higher prevalence in male patients than in female patients (n=203.65%; n=29.33%, respectively; p <0.001).

Of the total patients, 69.7% (n=278) presented with submissive hemoptysis, 22.3% (n=89) had minor hemoptysis, and 8% (n=32) had massive hemoptysis. Malignancy was the most common etiology in massive and minor hemoptysis groups, whereas TB sequela was the most common etiology in the submissive hemoptysis group. The most common histologic type of lung cancer was squamous cell carcinoma (27.4%). The demographic characteristics of the patients are shown in Table 1.

Malignancy was the most common cause of hemoptysis in the entire patient group (n=91, 22.8%), followed by TB sequela (n=76, 19%) and bronchiectasis (n=56, 14%). The etiologies of hemoptysis are shown in Table 2.

Table 1. Demographic and clinical characteristics of patients with hemoptysis

Characteristic	n	%
Sex, male	312	78.0
Age in years (median ± SD)	55.34 ± 16.09	
Comorbidities		
Hypertension	85	21.3
COPD	65	16.3
Coronary artery disease	49	12.3
Diabetes mellitus	42	10.5
Tobacco use (current and former)	295	73.7
Male	203	65.0
Female	29	33.0
Tuberculosis history	103	25.8
Drug use		
Vitamin K antagonist	24	6.0
Acetylsalicylic acid	28	7.0
Others	10	2.5
More than one	6	1.5
Amount of bleeding		
Submassive	278	69.7
Massive	32	8.0
Minor	89	22.3
Recurrent hospitalization	101	25.3

COPD: Chronic obstructive pulmonary disease; SD: Standard deviation

Table 2. Hemoptysis etiologies

Etiological diagnosis	n	%
Malignancy	91	22.8
Tuberculosis sequela	76	19.0
Bronchiectasis	56	14.0
Drug-induced	43	10.8
Active tuberculosis	27	6.8
Pneumonia	17	4.3
Pulmonary embolism	10	2.5
Hemorrhagic diathesis	7	1.8
Anthracosis	5	1.3
Foreign body aspiration	4	1.0
Aspergilloma	2	0.5
Acute bronchitis	2	0.5
Sarcoidosis	2	0.5
Cryptogenic	63	15.7

The most common etiologies of hemoptysis in female patients were bronchiectasis (n=25, 28.4%), drug-induced etiologies (n=13, 14.8%), and TB sequela (n = 8, 9.1%). In male patients, malignancy (n = 85, 27.2%), TB sequelae (n=68, 21.8%), and bronchiectasis (n=31, 9.9%) were the most frequent causes of hemoptysis. Different etiologies according to sex are described in Table 3. Drug-induced hemoptysis was noted in 68 of the 400 (17%) patients, making it the second most common etiology in female patients (14.8%) and the fourth most common etiology in male patients (9.6%). Obvious cause of hemoptysis was not found in 63 patients (15.7%) (cryptogenic).n total, 25% of patients required rehospitalization, and the most common etiologies of hemoptysis in these cases were TB sequelae (n=31, 30.7%) and malignancy (n=24, 23.8%).

Table 3. Relationships between etiological diagnosis and sex in patients with hemoptysis

	Female		Male		
Diagnosis	**n**	**%**	**n**	**%**	**p***
Bronchiectasis	25	28.4%	31	9.9%	<0.001
Tuberculosis sequelae	8	9.1%	68	21.8%	0.007
Malignancy	6	6.8%	85	27.2%	<0.001
Acute bronchitis	2	2.3%	0	0.0%	0.008
Drug-induced	13	14.8%	30	9.6%	0.17
Active tuberculosis	5	5.7%	22	7.1%	0.65
Pneumonia	4	4.5%	13	4.2%	0.88
Pulmonary embolism	4	4.5%	6	1.9%	0.16
Hemorrhagic diathesis	2	2.3%	5	1.6%	0.67
Anthracosis	2	2.3%	3	1.0%	0.33
Foreign body aspiration	1	1.1%	3	1.0%	0.88
Aspergilloma	0	0.0%	2	0.6%	0.45
Sarcoidosis	1	1.1%	1	0.3%	0.34
Cryptogenic	17	19.3%	46	14.7%	0.30

The p-values for those etiological diagnoses significantly associated with sex are shown in bold.

All patients in our sample underwent a chest X-ray and 69.8% (n=279) exhibited radiologic abnormalities. Of the 400 patients, 334 also underwent a chest CT scan and radiologic abnormalities were detected in 79.2% of these individuals. Abnormal findings were identified in 65.7% of the 202 patients who underwent FOB, and 89.5% of the 19 patients who underwent RB. A confirmed diagnosis was made using chest X-rays in 64.5% of the patients, chest CT in 83.6%, FOB in 24.8%, RB in 52.6%, and a combination of FOB and chest CT in 84.7%. Diagnosis of the cause of their hemoptysis was made in 84.7% of the patients, with the highest rate of diagnostic success achieved using a combination of CT and bronchoscopy.

Medications were used to treat 88.8% of the patients (n=355), whereas 6.5% (n=26) underwent BAE, 1.7% received endobronchial treatment, and 1.3% (n=5) underwent surgery for bleeding control. BAE was performed in 34 patients, and the most common etiology of hemoptysis in this group was TB sequela (n=16, 47%). The BAE's success rate in stopping bleeding was 76.5%. The rate of bleeding recurrence was higher in patients with hemoptysis caused by TB sequelae (n=31, 30.7%) and malignancy (n=24, 23.8%). Eleven patients underwent surgery to treat hemoptysis. Lobectomy was performed in 2.0% (n=8), pneumonectomy in 0.5% (n=2) and lung wedge resection in 0.3% (n=1). Hemoptysis was controlled with surgical treatment in five patients (one malignancy, one anthracosis, two aspergilloma, and one foreign body aspiration).

In total, 1% of patients (n=4) died during hospitalization, all with massive hemoptysis. The 2-6 year overall survival rate was 70.8% (95% confidence interval (CI): 60-81.6) in women and 56.1% (95% CI: 50.2-62) in men (p=0.005) (Figure 2). In this patient population, the analysis also identified several risk

factors associated with mortality, including malignancy, age >65 years, COPD history, and diabetes history. The hazard ratios, *p*-values, and 95% CIs for all covariables are displayed in Table 4.

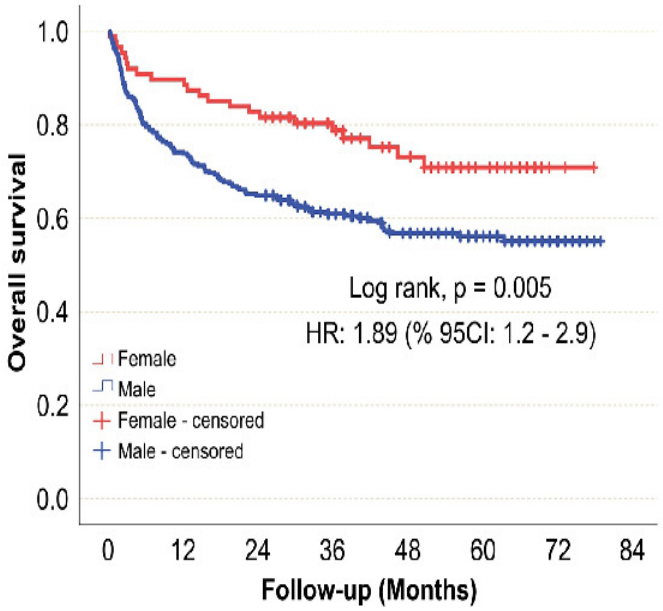

Figure 2. Cumulative hemoptysis survival rates of women and men calculated using the Kaplan Meier method. The patients were compared by sex using a log-rank test. The 2–6-year survival rates were 70.8% in women and 56.1% in men (p = 0.005)

Table 4. Results of a Cox regression mortality risk analysis of patients with hemoptysis based on age and comorbidities

Variable	p	Hazard ratio	95% CI Lower	95% CI Upper
Age >65 years	0.001	1.87	1.31	2.69
Pulmonary malignancy	<0.001	6.72	4.45	10.13
Diabetes mellitus	0.022	1.72	1.08	2.73
COPD	0.009	1.70	1.14	2.55
Bronchiectasis	0.57	0.82	0.43	1.60
Active tuberculosis	0.12	0.20	0.03	1.49
Atrial fibrillation	0.19	1.73	0.76	3.92
Hypertension	0.24	1.25	0.86	1.82
Chronic renal failure	0.97	1.02	0.36	2.86

The p-Values for those variables significantly associated with mortality are shown in bold.
CI: Confidence interval, COPD: Chronic obstructive pulmonary disease

DISCUSSION

The present study provides a comprehensive analysis of the etiologies, diagnostic modalities, treatment approaches, and prognostic factors associated with hemoptysis in a cohort of 400 patients. Given the extensive patient cohort involved, this study stands out in the literature. Our findings reveal that malignancy, particularly lung cancer, is the leading cause of hemoptysis, corroborating the trends observed in developed countries. This is contrasted with developing regions where tuberculosis and its sequelae remain predominant etiologies. Furthermore, the study highlights significant gender differences in the causes of hemoptysis, with bronchiectasis being more common in female patients and malignancy in male patients. The higher mortality rates observed in male patients underscore the need for heightened surveillance and prompt intervention, especially in those with comorbid conditions such as COPD, diabetes, and advanced age. These insights emphasize the importance of a tailored approach to managing hemoptysis, considering the underlying causes and individual patient characteristics to improve outcomes.

Malignancy was the leading cause of hemoptysis in our study. While some studies have ranked malignancy as the second, fourth, or fifth most frequent cause of hemoptysis, other studies, including the present study, have found it to be the leading cause.[2,4,10-13] Malignancy was the most common etiology in all participants, particularly in male patients and smokers. This highlights the importance of evaluating malignancy as a potential cause of hemoptysis in clinical settings, especially in these patients. This research revealed that squamous cell carcinoma was the most commonly occurring histologic type of lung cancer among patients with hemoptysis. Similarly, a 2018 study also identified squamous cell carcinoma as the predominant histologic type.[12] We attribute the increased prevalence of hemoptysis in patients with squamous cell carcinoma to the tumor's central location.

In this study, TB sequelae accounted for 19% of the etiologies among patients, which contrasts with some other studies that did not list this condition as a common cause.[4] However, two other studies reported that TB sequelae comprised 17.3% and 24% of the etiology.[11,14] The treatment of TB through direct observation has helped decrease the number of TB cases in Turkey, subsequently affecting the ratios of common etiologies in hemoptysis.[15] The increasing number of lung cancer cases in recent years is another influential factor that affects the hemoptysis etiology ratios.[16] We believe that due to the increasing number of cancer cases today, malignancies play a larger role in the etiology of hemoptysis. While tuberculosis-related hemoptysis cases have decreased due to the control of tuberculosis and advancements in treatment protocols, the incidence of lung cancer and other bronchopulmonary malignancies has increased due to modern lifestyles and environmental factors. In total, 25% of patients were hospitalized due to hemoptysis, with TB sequelae and malignancy being significant factors for recurrence. Therefore, close monitoring of these two patient groups for recurrence is necessary.

Bronchiectasis remains a prevalent health concern among women. This study identified bronchiectasis as the most common cause among women and the third most overall common cause. Sex-specific epidemiological, biological, and environmental variables influence the development of bronchiectasis, with a heavier disease burden in female patients.[17] A previous study found that 63.9% of those diagnosed with bronchiectasis are female, with postinfection illness being the predominant underlying cause.[18] Approximately 33% of the global population relies on solid fuels such as biomass and coal.[19] This has led to significant household air pollution, which poses substantial health risks, especially to women and children. The higher rate of bronchiectasis in female patients may be attributed to greater exposure to indoor air pollution compared to males. In male patients, we identified malignancy as the predominant cause, strongly associated with higher smoking rates. Therefore, it is crucial to conduct a detailed assessment to rule out cancer in patients with hemoptysis, particularly male patients with a history of smoking. Bronchiectasis should also be considered primarily in female patients who have been exposed to biomass or have a history of recurrent infections. Further research is warranted to investigate the differing factors underlying hemoptysis between the sexes.

Approximately 44% of our cases had diagnoses other than malignancy, bronchiectasis, and TB sequelae. In this study, cryptogenic hemoptysis occurred in 15.7% of the patients. Studies have reported varying rates of cryptogenic hemoptysis, ranging from 5.7%-50%.[20,21] While drug-induced hemoptysis is not commonly reported, it was the fourth most common etiology in this study, accounting for 10.8% of cases overall, and the second most common cause among female patients, accounting for 14.8%.[9,17] In recent years, the increased use of medications causing bleeding in cardiological treatments, coupled with inadequate monitoring of drug side effects in busy outpatient settings, may contribute to the rising incidence of drug-related hemoptysis. Given the potential challenges in early detection of drug side effects due to socio-cultural factors, clinicians should consider the possibility of drug-induced hemoptysis when evaluating patients presenting with this symptom.

In our study group, submissive hemoptysis was more prevalent than massive and minor hemoptysis, accounting for 69.7% of cases. This study observed massive hemoptysis in 8% of cases, with malignancy being the major cause. Similarly, malignancy was the most frequent cause in patients with minor hemoptysis. Since cancer may be a hidden cause of hemoptysis, a complete assessment is required regardless of the bleeding's intensity.[22] In this study, 30.2% of the patients presented with a normal chest X-ray; however, high-resolution chest CT detected bronchiectasis in 18.2%. Other studies have reported that 20%-40% of hemoptysis cases have normal chest X-ray findings, with bronchiectasis being the most common underlying pathology.[23,24]

In 88.8% of our patients, TXA and supportive treatment were effective to control bleeding. A study of a large cohort of patients with hemoptysis admitted to the emergency department found that the in-hospital mortality rate was significantly lower in patients receiving TXA compared with the control group, and was associated with a shorter hospital stay.[25] RB was performed on 19 patients in whom medical treatment failed to control bleeding. Among these patients, seven also received laser, argon plasma coagulation, and tumor debulking treatments. The number of patients who underwent surgery was small in our cohort. Five patients underwent surgical procedures including two with aspergilloma and one each with malignancy, anthracosis, and diesel fuel aspiration. Given the potential complications of surgery, it is advisable to opt for less invasive endobronchial therapy or BAE. A study found that BAE outperformed surgery in treating hemoptysis and recommended surgical treatment for patients not responding to BAE.[26] Surgical treatment should be considered when other treatments are not sufficient. BAE usage has grown since the study published by Remy et al.[27] in 1973. In our current study, the BAE treatment technique was administered to 34 patients (8.5%) through interventional radiology, and TB sequelae were diagnosed in 47% of these individuals. According to Tayal et al.,[28] 80% of patients undergoing BAE had TB sequelae. In our research, BAE effectively controlled bleeding in 76.5% of the patients. However, the bleeding recurrence rate was high in 61.8% of the patients (22/25) who reported recurrent bleeding, which was >57.7% stated by Fruchter et al.[29] Only one patient suffered from spinal ischemia, the most severe BAE consequence.

Hospitals' experience and capabilities, along with patient characteristics, can account for the varying mortality rates reported in different studies. Studies that only include patients with massive hemoptysis have often reported mortality rates as high as 30%–50%.[30,31] In a study of 8,240 patients with hemoptysis requiring hospitalization in the USA, the mortality rate during hospitalization was 4.5%, higher than that in the present study.[32] In this study, all patients who died (three with lung cancer and one with TB) had massive hemoptysis, resulting in a 1% mortality rate during hospitalization. The lower mortality rate in the present study can be attributed to the smaller number of patients with massive hemoptysis and the availability of an interventional pulmonology unit in our hospital. This study revealed a lower long-term overall survival rate among male patients. The 2–6-year survival rate was 70.8% for women and 56.1% for men. COPD, pulmonary malignancy, age >65 years, and a medical history of diabetes all affect survival rates. Other studies have also identified these risk factors, with malignancy being the most common factor influencing mortality.[33] Therefore, male patients with hemoptysis should receive close, long-term follow-up, especially if they also have a malignancy. This study has several limitations and strengths. The retrospective design and single-center setting may limit the generalizability of our findings. However, the large patient cohort enhances the study's robustness compared to other hemoptysis studies. We believe that this four-year dataset from our hospital, a reference center for chest diseases, provides valuable insights for future research. Nevertheless, prospective, multicenter studies are needed to confirm our findings and offer more comprehensive insights into the management of hemoptysis.

CONCLUSION

Our study, conducted at our leading chest disease center, sheds light on the etiologies, diagnostic approaches, treatment strategies, and prognostic factors associated with hemoptysis. Our findings underscore the importance of personalized management, taking into account individual patient characteristics and underlying causes, to improve outcomes. Clinicians should be mindful of the etiological factors, severity of hemoptysis, and risk factors influencing long-term survival rates. We believe this study offers valuable data for future research.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İstanbul Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (Date: 21.06.2016, Decision No: 2016/26).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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